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Cognitive Decline and Neuroprogression in Bipolar Disorder: a case for Hitchens' Razor.

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We are grateful to our colleagues (Duan et al. and Allot & Van Rheenen) for their commentaries on our recent meta-analysis that showed that longitudinal cognitive performance tends to be stable both in recent-onset and late-life bipolar disorder (BD)[1]. Although the two comments differ in their content, a main theme emerges from them: (i) given there are

methodological limitations to the studies included in our review, such as lack of adjustment for medication use and relatively short follow-up periods, hence (ii) cognitive decline (and consequently neuroprogression) cannot be ruled out either in all or in a subset of BD patients.

It has been consistently reported a relationship between the number of affective episodes, especially manic ones, and the magnitude of cognitive deficits in BD. This finding was frequently interpreted causally: that successive affective episodes would cause a cognitive deficit, and was subsequently included in multiple reviews as evidence supporting the neuroprogression hypothesis and staging models proposed for BD[2]. Some of us noticed at the time the unfeasibility of inferring such causal relationships from cross-sectional studies, suggesting that this association could as likely be indicating the existence of subgroups or patient profiles according to the severity of their clinical course[3]. That is, only longitudinal studies could possibly clarify the trajectories of cognitive deficits in BD.

More than ten years after neuroprogression and staging models for BD were proposed, the overwhelming majority of longitudinal studies seem to show that cognitive deficits are stable rather than progressive[1,4]. At this point, we agree with the comments of Duan et al. and Allot & Van Rheenen on the limitations of the longitudinal studies currently available: we need future research with longer follow-up periods, or with a greater focus on cognitive heterogeneity or exposure to medications. However, we also want to make a point here. Rather than concluding that these limitations do not allow us to rule out the concept of cognitive decline (and neuroprogression), we would like to emphasize that, to this day, it is difficult to find any empirical evidence that can support it.

To illustrate this point, we invoke Hitchens' razor, namely, an epistemological razor expressed by writer Christopher Hitchens[5]. It says that the burden of proof regarding the truthfulness of a claim lies with the one who makes the claim. If this burden is not met, then the claim is unfounded, and its opponents need not argue further in order to dismiss it. This claim can be traced to as early as 1704 where Pritius wrote to Artemon: "How can you prove it, Artemon? Because you asserted it without cause, therefore also it may be denied without cause". Paradoxically, it seems that the Hitchens' razor has dramatically inverted and the conventional view

is that BD follow a progressive cognitive decline. Apparently, this will remain the case until someone is able to prove otherwise in an unpollutable and unquestionable fashion.

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